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THE SIMULATION OF CONTROLING THE SPREAD OF HIV USING ANALYTICAL AND NUMERICAL APPROACH

Miksalmina, Said Munzir and Tarmizi

Abstract. *This research is related to the optimal control problem in controlling the spread of HIV (Human Immunodeficiency Virus) to minimize the amount of HIV virus and treatment costs. The solution of the problem in this is conducted by the analytical and numerical approaches. The solution is initially conducted analytically through linearization of state equations around equilibrium point, while the second solution is conducted numerically using the direct discretization method with pseudospectral approach. The analytical solution procedure using Pontryagin Minimum Principle with the help of MATLAB symbolic features, while numerical solution using Gaus Pseudospectral Method (GPM) with the help of TOMLAB/PROPT. The results of numerical simulations for controlling the spread of the HIV virus to the initial time $t_0 = 0$ and the final time $t_f = 500$ successfully minimize mutant HIV strain, proviral Th cells infected by the mutant strain , and Th cells productively infected by the new strain as well as minimizing the cost of therapy is needed. The optimal solution indicates an increase in uninfected Th cells and a decrease in wild-type HIV, proviral Th cells (wild type), productively infected Th cells (wild type), mutant HIV strain, proviral Th cells infected by the mutant strain and Th cells productively infected by the new strain. These results showed a significant difference with the analytical solution. There are many potential differences in the results, including as a result of linearization at the equilibrium point and the condition number for the matrix involved in the analytic solution.*

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1. INTRODUCTION

Acquired Immuno Deficiency Syndrome (AIDS) is an infectious disease caused by a virus called Human Immuno Deficiency Virus (HIV). HIV (Human Immunodeficiency Virus) is a virus that attacks the human immune system. This disease is a dangerous disease and should be aware because it spread rapidly around the world [9]. One approach for explaining the solution of the problems of the spread of the HIV virus that occur in the real world is to translate the problem into mathematical language

According to Setiawan [9], by translating problems into mathematical language it will obtain a mathematical models, which describe the results of the formulation of the problem to be solved. Mathematical models can be applied to determine the spread of the HIV virus. The purpose of modeling is to control the spread of the HIV virus where its complexity tends to increase.

Various attempts were made to control the spread of the HIV virus. One of them is the solution of drug therapy. Fariana [4] have conducted an analysis of stability and optimal control of drug therapy in the treatment of HIV with Highly Active Anti-Retroviral Therapy (HAART). HAART is a method of treatment which is performed in patients with HIV that aims to slow the progres of HIV infection to AIDS.

Research results show the effectiveness of drug control to suppress the development of the HIV virus with the provision of Anti Retroviral Drugs (ARVs). ARV is a drug that works inhibit HIV replication in CD4 (white blood cells), so as to reduce the amount of virus in the blood.

The results of two studies conducted by Fariana [4] and Sukokarlinda, et al (2013) provide a solution that is not optimal. This is due to HAART and the provision of antiretroviral drugs can not eliminate the life cycle strains (strains) of HIV in a population vary widely and can cause serious side effects. Therefore, it is necessary to control the spread of HIV in other ways.

Stengel [11] has conducted a simulation control of HIV by developing a model of Perelson, et al [1] and Kirschner, et al [3] in the form of four dynamic equations. This model was then developed into seven dynamic equations which describe some therapies as the treatment.

Based on previous studies, the authors would like to continue the research in terms of controlling the spread of the HIV virus. This study adopts a model studied by Stengel [11] and Afandi [2]. The model minimizes the number of malignant and mutant viruses as well as the cost of therapy.

The model is solved by analytical and numerical approaches. Analytic approach is solved with the help of MATLAB symbolic, while the numerical approximation is solved with the helping TOMLAB/propt.

2. METHODS

Research activities include study design, study subjects, research procedures and research instruments. The design of the research conducted in this research is to collect research materials including sources of information both journals, books articles and other relevant instructions. In this case study refers to internasionl journal entitled Mutation and control of the human immudeficiency virus written by Robert F. Stengel [11]. In this case study refers to internasionl journal entitled Mutation and control of the human immudeficiency virus written by Robert F. Stengel [11]. The journal reference used is a journal with the title Dynamics of HIV infection of CD4+T Cells by Perelson [1] and Optimal control of the chemotherapy of HIV by Kirschner [3] and Strategy Control the spread of HIV wild type and mutant therapy with inhibitors by Afandi [2]. The subject of research in this paper is to analyze the results Stengel [11] using simulation TOMLAB/propt. Besides understanding the theories that support the discussion of optimal control problems that include: Pontryagin Minimum Principle, Gauss Pseudospectral Method (GPM), the program TOMLAB/propt and symbolic methods.

Troubleshooting control the spread of HIV in this study through analytical and numerical approaches. analytical solution performed with linearized equation of state around the equilibrium point with the help of MATLAB symbolic. While the settlement is done numerically by direct discretization using pseudospectral method with the help TOMLAB/propt.

Simulations done with therapy and no therapy for optimal control problems in controlling the spread of HIV is done with the initial time $t_0 = 0$ and the final time $t_f = 500$, the value of the control variable for therapy u_1, u_2, u_3, u_4 ranges between 0 and 1. Simulation is done to control the spread of HIV processing time for 500 days.

Simulations are also carried out with a view to minimizing the number of objective function the mutant HIV strain (x_5), proviral T_h cells infected by the mutant strain (x_6), and T_h cells productively infected by the new strain (x_7) as well as the cost of therapy. While the control variable is therapy *protease inhibitor* (u_1), *fussion inhibitor* (u_2), T_h *cell enhancer* (u_3) and *reverse trancription inhibitor* (u_4). This simulation is done by using

the parameter initial values of the state variables are different, using the parameter values of the journal Stengel [11].

3. RESULTS

Dynamic system used in this study consisted of seven differential equations, each of which express a mathematical model consisting of : wild-type HIV, uninfected T_h cells, proviral T_h cells (wild type), productively infected T_h cells (wild type), mutant HIV strain, proviral T_h cells infected by the mutant strain and T_h cells productively infected by the new strain. System of differential equations describe the spread of the HIV virus and the type of therapy as control variables are given by the following dynamical system [11]:

$$\begin{aligned}
\dot{x}_1 &= a_1x_1 - a_2x_1x_2(1-u_2) + a_3a_4x_4(1-a_{10})(1-u_1) \\
\dot{x}_2 &= \frac{a_5}{1+x_1+x_5} - a_2x_1x_2(1-u_2)(1-u_4) - a_6x_2 - a_2a_{11}x_2x_5 \\
&\quad + a_7\big(1 - \frac{x_2+x_3+x_4+x_6+x_7}{a_8}\big)x_2(1+u_3) \\
\dot{x}_3 &= a_2x_1x_2(1-u_2)(1-u_4) - a_9x_3 - a_6x_3 \\
\dot{x}_4 &= a_9x_3 - a_4x_4 \\
\dot{x}_5 &= a_3a_4a_{10}x_4 + a_3a_4x_7 - a_1x_5 - a_2a_{11}x_5x_2 \\
\dot{x}_6 &= a_2a_{11}x_5x_2 - a_9x_6 - a_6x_6 \\
\dot{x}_7 &= a_9x_6 - a_4x_7
\end{aligned} \tag{1}$$

with

$\dot{x}_1$ = Wild-type HIV
$\dot{x}_2$ = Uninfected T_h cells
$\dot{x}_3$ = Proviral T_h cells (wild type)
$\dot{x}_4$ = Productively infected T_h cells (wild type)
$\dot{x}_5$ = Mutant HIV strain
$\dot{x}_6$ = Proviral T_h cells infected by the mutant strain
$\dot{x}_7$ = T_h cells productively infected by the new strain
a_1 = The average particle death
a_2 = Constant average healthy cells become infected
a_3 = The amount of HIV virus produced
a_4 = Average mortality $\dot{x}_4$
a_5 = Sources of healthy cells
a_6 = Average mortality $\dot{x}_1$ and $\dot{x}_3$
a_7 = The average growth of healthy cells
a_8 = The maximum level of healthy cells
a_9 = Average of infected cells become productive
a_{10} = The mutation rate
a_{11} = The mutant strain has a fitness
u_1 = Protease inhibitor
u_2 = Fussions inhibitor
u_3 = T_h cells enhancer
u_4 = Reverse trancription inhibitor

System of differential equations (1) above is referred to as equation of state (state equation). Each differential equations dynamical systems above have the initial conditions and final time (t_f) is determined. *Fix In this study, variations in circumstances that meet the type of control system ed-final time and free-final state system*, where $x(t_0) = x_0$ dan $x(t_f) = x_f$ free.

Optimal Control Solution

Optimal control problems in this research is to minimize the number of malignant and mutant viruses as well as the cost of therapy are formulated in the objective function as follows:

$$J[x(t), u(t)] = \frac{1}{2}\Big[S_{f55}x_5(t_f)^2 + S_{f66}x_6(t_f)^2\Big] + \frac{1}{2}\int_{t_0}^{t_f}\Big[q_{55}x_5(t)^2 + q_{66}x_6(t)^2 + q_{77}x_7(t)^2 + ru_i(t)^2\Big]dt \quad (2)$$

Where the value of u is taken from the set u, $u \in U = \{u(t)|0 \leq u \leq 1, 0 \leq t \leq t_f\}$. In this case, u as $(0 \leq u \leq 1)$ is a measure of the medical business (with the upper limit of 1 and the rate of medical efforts made proportionally from the amount of HIV virus). Equation (2) shows r is a variable that is correlated with weight control usage costs (cost control) is a balancing factor of cost control system. whereas $S_{f55}, S_{f66}, S_{f77}, q_{55}, q_{66}, q_{77}$ is a diagonal matrix elements are presented in equation (2) which states that permitted reciprocal relationship between the values of the response to the charges, with the aim of balancing the speed and efficacy of treatment, in this case will look for a minimum function.

Analytical methods

Optimal treatment strategy is obtained by solving the optimality system, consisting of fourteen ordinary differential equation of state and costate equations. The settlement resolved by designing a symbolic program MATLAB, by first linearized seven state equation.

1. Around Equilibrated point linearization

To liniarized seven state equation then determined equilibrium point, where $x_1^* = x_3^* = x_4^* = x_5^* = x_6^* = x_7^* = 0, x_2^* = 1000$ and assumed $u_1^* = u_2^* = u_3^* = u_4^* = 0$ thus obtained form a linear system. By using the Taylor series approach the equation system around the equilibrium point is

$$\begin{aligned} F(x,u) &= f(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(x_1 - x_1^*)\frac{\partial f}{\partial x_1}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(x_2 - x_2^*)\frac{\partial f}{\partial x_2}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(x_3 - x_3^*)\frac{\partial f}{\partial x_3}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(x_4 - x_4^*)\frac{\partial f}{\partial x_4}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(x_5 - x_5^*)\frac{\partial f}{\partial x_5}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(x_6 - x_6^*)\frac{\partial f}{\partial x_6}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(x_7 - x_7^*)\frac{\partial f}{\partial x_7}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(u_1 - u_1^*)\frac{\partial f}{\partial u_1}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(u_2 - u_2^*)\frac{\partial f}{\partial u_2}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(u_3 - u_3^*)\frac{\partial f}{\partial u_3}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\ &+(u_4 - u_4^*)\frac{\partial f}{\partial u_4}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \end{aligned} \quad (3)$$

Based on the equation (3) above obtained results linearized state equation as follows:

$$
\begin{aligned}
\frac{dx_1}{dt} &= x_1(-a_1 - a_2x_2) + x_4\big(a_3a_4(1 - a_10)\big) \\
\frac{dx_2}{dt} &= a_5 - a_6x_2 + a_7\big(1 - \frac{x_2}{a_8}\big)x_2 + x_1\big(- (a_5 + a_2x_2)\big) \\
&\quad +(x_2 - x_2^*)\big((-a_6) - \frac{a_7x_2}{a_8} + a_7(1 - \frac{x_2}{a_8})\big) + x_3\big(\frac{a_7x_2}{a_8}\big) \\
&\quad +x_4\big(\frac{a_7x_2}{a_8}\big) + x_5\big(- (a_5 + a_2a_{11}x_2)\big) + x_6\big(\frac{a_7x_2}{a_8}\big) + x_7\big(\frac{a_7x_2}{a_8}\big) \\
&\quad +u_3\big(a_7x_2a_7\big(\frac{x_2 + x_3 + x_4 + x_6 + x_7}{a_8}\big)x_2\big) \\
\frac{dx_3}{dt} &= x_1(a_1x_2) + x_3(-(a_9 + a_6)) \\
\frac{dx_4}{dt} &= x_3(a_9) + x_4(-a_4) \\
\frac{dx_5}{dt} &= x_4(a_3a_4a_{10}) + x_5(-a_1 - a_2a_{11}x_2) + x_7(a_3a_4) \\
\frac{dx_6}{dt} &= x_5(a_2a_{11}x_2) + x_6(a_9 - a_6) \\
\frac{dx_7}{dt} &= x_6(a_9) + x_7(a_4)
\end{aligned}
$$

Results linearization of equation (4) above, then solved using Pontryagin minimum principle with the help of MATLAB symbolic program, in order to obtain the general solution of the homogeneous and non- homogeneous equations. Final solution of this problem is obtained as follows:

$$
\begin{aligned}
x_1^* &= -0.4347e^{-0.0041t} + 2.8115 \times 10^{-13}e^{0.0041t} + 0.2837e^{0.0079t} \\
&\quad +0.3421e^{-0.0079t} + 4.1356 \times 10^{-15}e^{-2.4120t} + 1.2664 \times 10^{-52}e^{0.2635t} \\
&\quad +0.2000e^{-0.2745t} - 6.7672 \times 10^{-57}e^{0.2745t} + 2.545 \times 10^{-34}e^{2.4204t} \\
x_2^* &= 2.3902 \times 10^{18}e^{-0.0300t} + 0.2448e^{-2.4120t} + 2.1825 \times 10^{-34}e^{0.2745t} \\
&\quad -2.7789e^{-0.2635t} + 54.7776e^{0.0041t} - 4.78083 \times 10^{18}e^{0.0300t} \\
&\quad -2.3902 \times 10^{18}e^{0.0300t} + 60.9346e^{2.4204t} + 191.9484e^{-0.0041t} \\
&\quad -124.3225e^{0.0079t} - 193.4611e^{-0.0079t} - 0.2275e^{-2.4120t} \\
&\quad +9.6902 \times 10^{51}e^{0.2635t} + 10.8370e^{-0.2745t} + 6.1951 \times 10^{-57}e^{0.2745t} \\
&\quad +1.0277 \times 10^{-}3e^{2.4204t} + 1000
\end{aligned}
$$

$$
\begin{aligned}
x_3^* &= 0.2200e^{-0.0079t} + 2.0342 \times 10^{13} e^{0.0041t} + 0.1343e^{-0.0041t} \\
&\quad -0.3220e^{-0.0079t} + 1.4630 \times 10{-}17e^{-2.4120t} - 6.6541 \times 10^{-52} e^{0.2635t} \\
&\quad +0.0017e^{-0.2745t} + 9.4611 \times 10^{-57} e^{0.2745t} - 2.5481 \times 10^{-36} e^{-2.4204t} \\
x_4^* &= 2.0342 \times 10^{-}13e^{0.0041t} - 0.0029e^{-0.0041t} + 0.0027e^{0.0079t} + 0.0028e^{-0.0079t} \\
&\quad -1.8932 \times 10^{-}19e^{-2.4120t} - 2.3606 \times 10{-}54e^{0.2635t} + 0.0017e^{0.2745t} \\
&\quad +2.7964 \times 10^{-59} e^{0.2745t} + 3.5060 \times 10^{-39} e^{-2.4204t} \\
x_5^* &= -0.2071e^{0.0041t} - 0.0671e^{-0.0041t} + 0.1865e^{0.0079t} + 0.0773e^{0.0079t} - 0.0541e^{-2.4120t} \\
&\quad -1.3330 \times 10^{52} e^{0.2635t} + 0.0645e^{-0.2745t} - 1.2014 \times 10^{-35} e^{-2.4204t} \\
x_6^* &= -0.1415e^{0.0041t} - 0.0795e^{-0.0041t} + 0.1076e^{0.0079t} + 0.1166e^{-0.0079t} \\
&\quad +3.2531 \times 10^{-4} e^{-2.4120t} - 6.5957 \times 10{-}54e^{0.2635t} - 0.0036e^{-0.2745t} \\
&\quad +2.2545 \times 10^{-58} e^{0.2745t} + 7.1983 \times 10^{-38} e^{-2.4204t} \\
x_7^* &= 0.0017e^{0.0041t} - 2.1395 \times 10^{-4} e^{0.0041t} + 0.0013e^{0.0079t} \\
&\quad +3.3760 \times 10^{-4} e^{-0.0079t} - 4.4933 \times 10^{-7} e^{-2.4120t} - 8.2012 \times 10^{-55} e^{0.2635t} \\
&\quad +3.1349 \times 10^{-4} e^{-0.2745t} + 1.4838 \times 10^{-59} e^{0.2745t} - 9.9040 \times 10^{41} e^{-2.4204t} \\
u_1^* &= 0 \\
u_2^* &= 0 \\
u_3^* &= 0
\end{aligned}
$$

Of the general solution can chart of satay and control variables are presented in Figure 1 and Figure 2 as follows:

Figure 1 shows that the number of wild-type HIV, uninfected T_h cells, proviral T_h cells (wild type), productively infected T_h cells (wild type), mutant HIV strain, proviral T_h cells infected by the mutant strain and T_h cells productively infected by the new strain.

Figure 2 shows the therapy of *protease inhibitor, fussion inhibitor*, T_h cells enhancer, *reverse trancription inhibitor* is static. It indicates that the four therapeutic fixed and unchanged.

2. Linearization point Optimal Numerical Results

In this case, the point of which is used for seven linearized state equation that the optimal point TOMLAB results, where $x_1^* = 0.001988$, $x_2^* = 983.68099$, $x_3^* = 0.00568$, $x_4^* = 0.00025$, $x_5^* = 0.007212$, $x_6^* = 0.003196$, $x_7^* = 0.39 \times 10^{-4}$ and $u_1^* = 0.365782$, $u_2^* = 1$, $u_3^* = 1$, $u_4^* = 1$, thus obtained form a linear system. By using the Taylor series approach the equation system around the equilibrium point is:

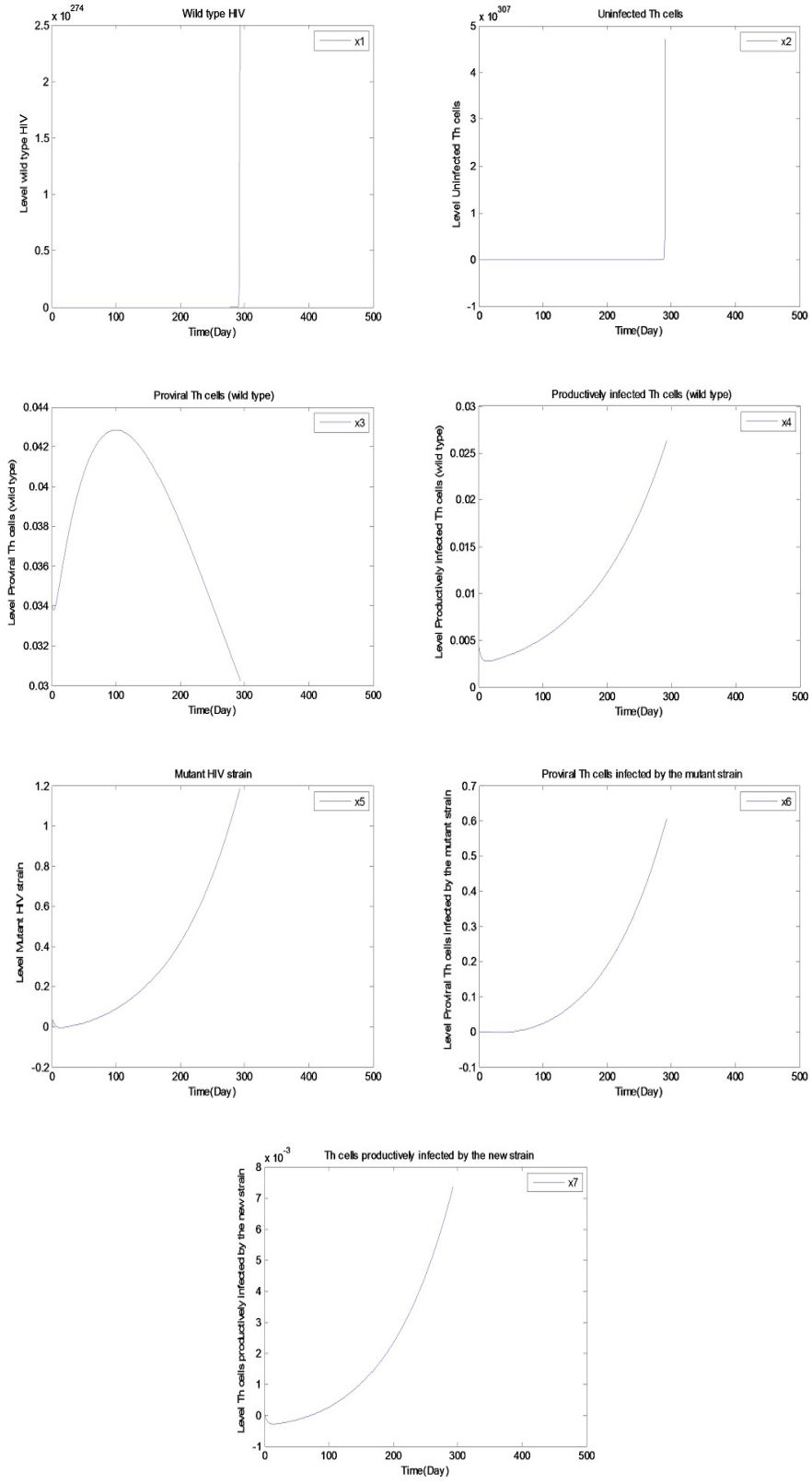


Figure 1: Analytical Solutions at State Variables in Point Equilibrated

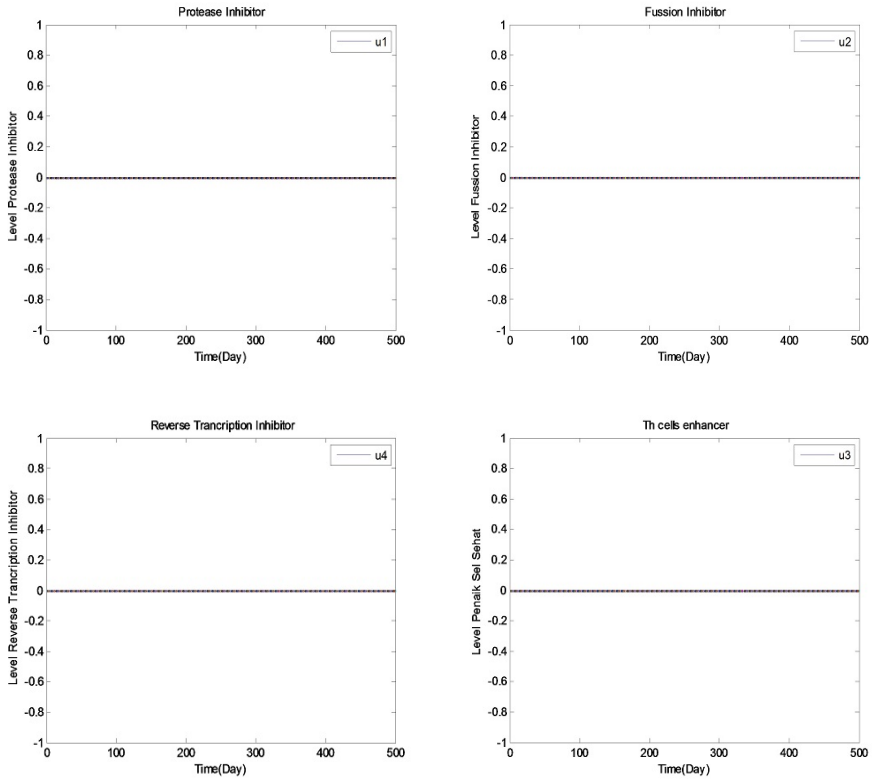


Figure 2: Analytical Solutions In Control

$$
\begin{aligned}
F(x,u) = \quad & f(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(x_1 - x_1^*)\frac{\partial f}{\partial x_1}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(x_2 - x_2^*)\frac{\partial f}{\partial x_2}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(x_3 - x_3^*)\frac{\partial f}{\partial x_3}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(x_4 - x_4^*)\frac{\partial f}{\partial x_4}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(x_5 - x_5^*)\frac{\partial f}{\partial x_5}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(x_6 - x_6^*)\frac{\partial f}{\partial x_6}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(x_7 - x_7^*)\frac{\partial f}{\partial x_7}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(u_1 - u_1^*)\frac{\partial f}{\partial u_1}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(u_2 - u_2^*)\frac{\partial f}{\partial u_2}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(u_3 - u_3^*)\frac{\partial f}{\partial u_3}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \\
& +(u_4 - u_4^*)\frac{\partial f}{\partial u_4}|(x_1^*x_2^*x_3^*x_4^*x_5^*x_6^*x_7^*, u_1^*u_2^*u_3^*u_4^*) \qquad (4)
\end{aligned}
$$

Based on the equation (4) in the above obtained results linearized state equation as follows:

$$
\begin{aligned}
\frac{dx_1}{dt} = \quad & -0.001988a_1 + 1.5855 \times 10^{-4}a_3a_4(1-a_{10})(1-u_1^*) \\
& +(x_1 - x_1^*)(a_1 - a_2x_2^*) + (x_4 - x_4^*)a_3a_4(1-a_{10})(1-u_1^*) \\
\frac{dx_2}{dt} = \quad & \frac{a_5}{984.6830} - 983.68099a_6 - 7.0943a_2a_{11} \\
& +1.9674 \times 10^3 a_7\Big(1 - \frac{983.6902}{a_8}\Big) + (x_1 - x_1^*)\Big(-\frac{a_5}{1.0185}\Big) \\
& +(x_2 - x_2^*)(-a_6 - 0.007212a_2a_{11}) + a_7\Big(1 - \frac{983.6902}{a_8}\Big) \\
& +a_7(1-983.6902a_8)+x_3-x_3^*-1.9674\times10^3a_7a_8+(x_4-x_4^*) \\
& -1.9674\times10^3a_7a_8+(x_6-x_6^*)-1.9674\times10^3a_7a_8+(x_7-x_7^*) \\
& -1.9674\times10^3a_7a_8+u_3-1983.68099a_7(-1.9674\times10^3a_7a_8)) \\
\frac{dx_3}{dt} = \quad & -0.00568a_9 - 0.00568a_6 + (x_3 - x_3^*)a_9 - (x_4 - x_4^*)a_4 \\
\frac{dx_4}{dt} = \quad & 0.00568a_9 - 0.00025a_4 + (x_3 - x_3^*)a_9 - (x_4 - x_4^*) \\
\frac{dx_5}{dt} = \quad & 0.00025a_3a_3a_{10} - a_1 + 0.39 \times 10^{-4}a_3a_4 - 0.007212a_1 \\
& -7.0943a_2a_{11}-(x_2-x_2^*)(0.007212a_2a_{11})+(a_4-a_4^*)a_3a_4a_{10} \\
& +(x_5 - x_5^*)(-a_1 - 983.68099a_2a_{11}) + (x_7 - x_7^*)a_3a_4 \\
\frac{dx_6}{dt} = \quad & 7.0943a_2a_{11} - 0.003196a_9 - 0.003196a_6 \\
& +(x_2 - x_2^*)(0.007212a_2a_{11}) + (x_6 - x_6^*)(-a_9 - a_6) \\
\frac{dx_7}{dt} = \quad & 0.0003196a_9 - 0.39 \times 10^{-4} + (x_6 - x_6^*)a_9 + (x_7 - x_7^*)a_4 \qquad (5)
\end{aligned}
$$

The results of the system linearized equation (5) above, then solved using Pontryagin Minimum Principle with the help of MATLAB symbolic program, n order to obtain the general solution of the homogeneous and non-homogeneous equations. The solution of equations obtained is then

determined value symbolic constants with the help of the program. Final solution of this problem is obtained as follows:

$$
\begin{aligned}
\dot{x}_1 &= -0.0322e^{-0.0230t} - 0.2344e^{-0.2400t} + 0.0040 \\
\dot{x}_2 &= 0.1766e^{-0.2564t} + \inf e^{0.2564t} - 1.0572 \times 10^{12}e^{-0.0438t} + \\
&\quad \inf e^{0.0438t} + \inf e^{0.0138t} - 3.1718 \times 10^5 e^{0.0138t} + 1.8817 \times \\
&\quad 10^{13}e^{2.3764t} + \inf e^{-0.2400t} - \inf e^{-0.0230t} - \inf e^{0.2564t} + \\
&\quad \inf e^{0.0138t} + 0.4699e^{2.4123t} - 3.3977 \times 10^9 e^{-0.2564t} - \\
&\quad \inf e^{0.0438t} + \inf e^{-2.4123t} + \inf e^{0.0438t} + \inf e^{0.0138t} + \\
&\quad inf e^{-0.0138t} + 58.6435e^{-0.2400t} - 193.3093e^{-0.0230t} - \\
&\quad 1.8817 \times 10^{13}e^{2.3764t} + 6.5185 \times 10^4 \\
\dot{x}_3 &= 4.7033 \times 10^{-27}e^{-0.0230t} \\
\dot{x}_4 &= 0.0037e^{-0.2400t} + 4.7004 \times 10^{-4}e^{0.0230t} \\
\dot{x}_5 &= 8.4627 \times 10^{-9}e^{2.4123t} + \inf e^{0.0138t} + \inf e^{0.2564t} - 1.1103 \times \\
&\quad 10^3 e^{0.2564t} + \inf e^{0.0438t} + \inf e^{-2.4123t} + \inf e^{-0.0438t} - \\
&\quad \inf e^{-}0.0138t + 0.0523e^{0.2400t} + 0.0014e^{-0.0230t} + 3.3933 \times \\
&\quad 10^5 e^{2.3764t} - 0.7324 \\
\dot{x}_6 &= \inf e^{0.0138t} + \inf e^{0.2564t} + 1.9988 \times 10^{-8}e^{2.4123t} + 1.5792 \times \\
&\quad 10^3 e{-}0.2564t - \inf e^{0.0438t} - \inf e^{-2.4123t} - \inf e^{0.0438t} + \\
&\quad \inf e^{-0.0138t} - 0.0034e^{-0.2400t} + 0.0031e^{-0.0230t} - 8.1245 \times \\
&\quad 10^5 e^{2.3764t} - 0.1612 \\
\dot{x}_7 &= 9.5439e^{0.2564t} - \inf e^{0.0138t} + 0.2760e^{2.4123t} + \inf e^{0.2564t} + \\
&\quad \inf e^{0.0438t} + \inf e^{0.0438t} - \inf e^{-0.0138t} + 2.1493 \times \\
&\quad 10^{-5}e^{-0.2400t} - 3.5308 \times 10^{-5}e - 0.0230t - 1.1409 \times \\
&\quad 10^3 e^{2.3764t} + 0.0022 \\
\dot{u}_1 &= 0 \\
\dot{u}_2 &= 0 \\
\dot{u}_3 &= 1.0158{\times}10^3(\inf e^{0.2564t}{+}\inf e^{0.0138t}{+}1.1076{\times}10^4 e^{2.4123t}{+} \\
&\quad 7.7844 \times 10^4 e^{-0.2564t} - \inf e^{0.0438t} - \inf e^{-2.4123t} - 1.5671 \times \\
&\quad 10^{-7}e^{-0.0438t} + \inf e^{-0.0138t} - 0.0015e^{-0.2400t} + 2.5702 \times \\
&\quad 10^{-5}e^{-0.0230t} + 348.9492e^{2.3764t} + 0.1105) \\
\dot{u}_4 &= 0
\end{aligned}
$$

Of the general solution can chart of state and control variables are presented in Figure 3 and Figure 4 as follows:

Figure 3 shows that the proviral T_h cells and productively infected Th cells (wild type) decreased. While Figure 4 shows the protease inhibitor, fussion inhibitor, and reverse trancription inhibitor therapy is static. This indicates that the three therapy fixed and unchanged.

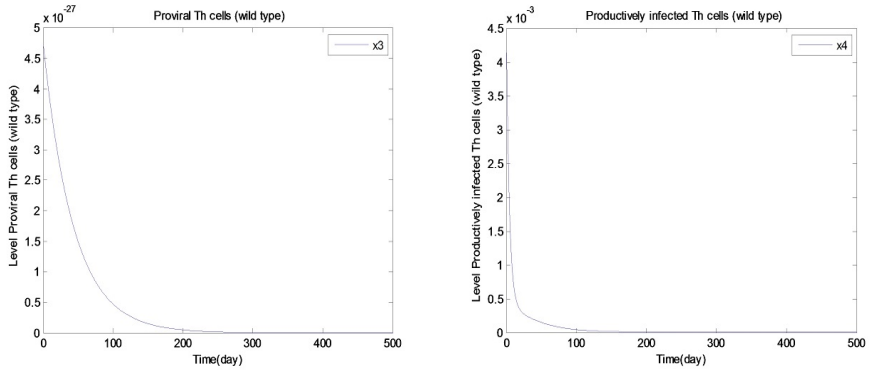


Figure 3: Analytical Solutions At state variables On Optimal Point Numerical Results

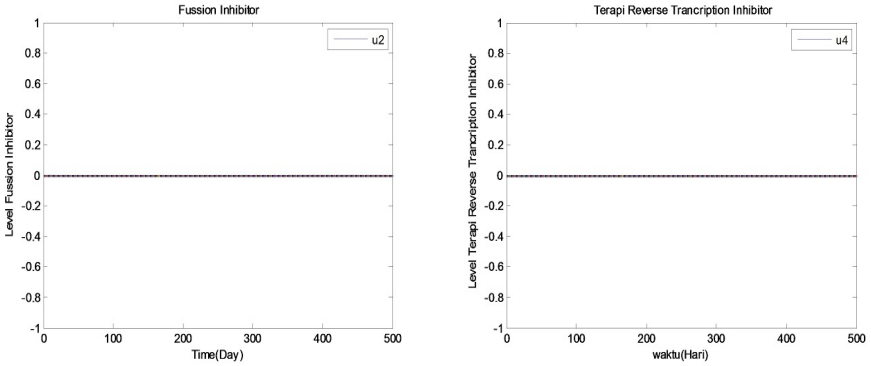


Figure 4: Analytical Solutions In Control

Table 1: Initial Condition Variable State [11]

Parameters	Value Estimates
x_1	0.049
x_2	904
x_3	0,034
x_4	0,0042
x_5	0
x_6	0
x_7	0
a_1	2,4
a_2	0,000024
a_3	1200
a_4	0,24
a_5	10
a_6	0,02
a_7	0,03
a_8	1500
a_9	0,003
a_10	0.1
a_11	0,6

Numerical Simulation and Analysis of Results

Completion of optimal control problems controlling the spread of the HIV virus using the direct method is based on the transformation of the optimal control problem into a problem of Non Linear Programming (NLP) with the state equation and the equation discretization control using pseudospectral method. Problem solving optimal control the spread of the HIV virus is done by using propt-MATLAB Optimal Control Software is TOMLAB/propt Optimization, which run on MATLAB software 7.10.0 (R2010a) is a toolbox that implements the method parameterization approach control variables that can be used to solve the NLP problem.

To be able to perform simulations of optimal control problems controlling the spread of the HIV virus by using TOMLAB/propt, required values of the parameters of the dynamic system models are presented in Table 1.

Based on the values of the parameters in Table 1, subsequently entered

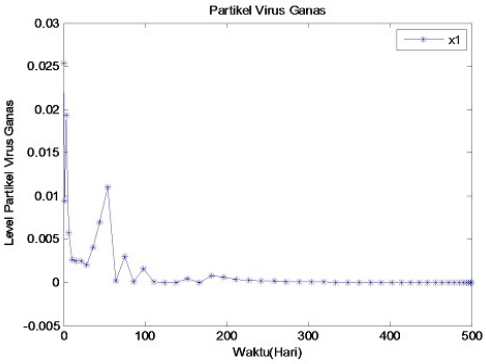
into the program TOMLAB/propt thus obtained simulation. Simulation for optimal control problems spread of the HIV virus carried by the initial time $t - 0 = 0$ and final time $t_f = 500$, the value of the control variable for therapy u_1, u_2, u_3, u_4 ranges between 0 and 1 Simulations performed with the initial value $_1 = u_2 = u_3 = u_4 = 1$ and the level of resistance mutants $a_{11} = 0.6$.

Figure 5. (i) indicates that the population of malignant viral particles decreases from the maximum point of 0.0253 to the minimum point 0 so achieve stability until day 500. Figure 5. (ii) shows that the number of healthy cells / uninfected Increased to 998.6436. Figure 5. (iii) indicates that the number of malignant virus-infected cell population plummeted to about 200 days, and then tended to be stable until day 500. Figure 5. (iv) shows that the number of malignant viruses and productive population also decreased to about 100 the first day, then tended to be stable until day 500. Figure 5. (v) shows that the population of mutant viral particles tended to decrease from the maximum point of 0.0228 towards 0.0055 minimum point. Figure 5. (vi) shows that the number of mutant virus-infected cell population experienced a steady increase until the first 100 days, then decreased gradually until day 500 by 2.6×10^3.

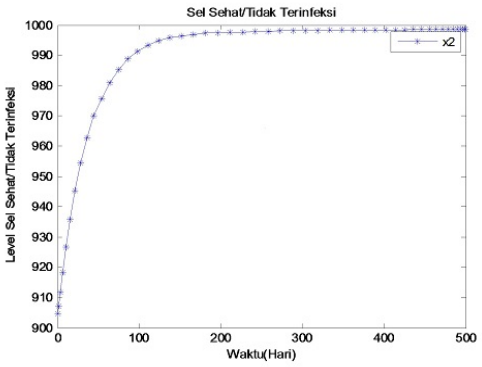
Figure 6. (i) indicates that the protease inhibitor therapy in the form of bang-bang (control function experienced a jump between 0 and 1) and fluctuated from 1 to the maximum point of the minimum point 0 and back again to the point of maximum 1. This indicates the power of therapy in suppressing and controlling cell growth of the HIV virus, thus toward equilibrium. While Figure 6. (ii), 6. (Iii) and 6 (iv) shows in a static state, meaning fussion inhibitor therapy, therapy riser healthy cells and reverse trancription inhibitor therapy fixed and unchanged. This indicates the power of therapy in controlling the growth of the HIV virus so that in a static state.

4. CONCLUSIONS

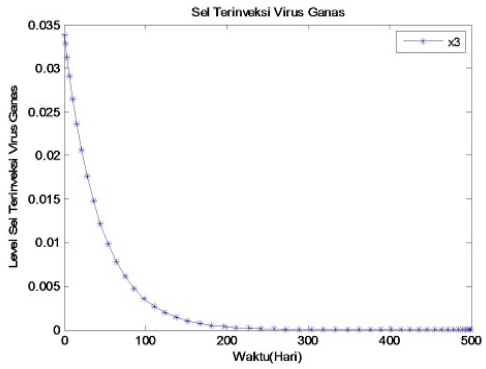
Simulation results Simulation analytic linearization equilibrium point is not defined on the results wild-type HIV, uninfected T_h cells , proviral T_h cells (wild type), productively infected T_h cells (wild type), mutant HIV strain, proviral T_h cells infected by the mutant strain and T_h cells productively infected by the new strain. While the optimal linearization point numerical results also provide results not defined, except in proviral T_h cells (wild type), productively infected T_h cells (wild type) decreased. The results



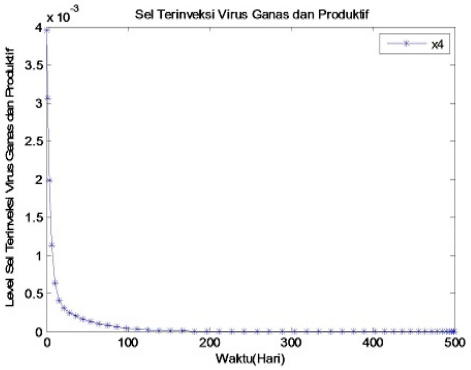
(i) wild-type HIV (x_1)



(ii) uninfected T_h cells (x_2)

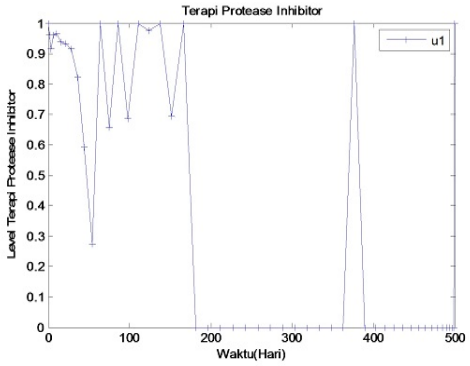


(iii) Proviral T_h cells (wild type) (x_3)

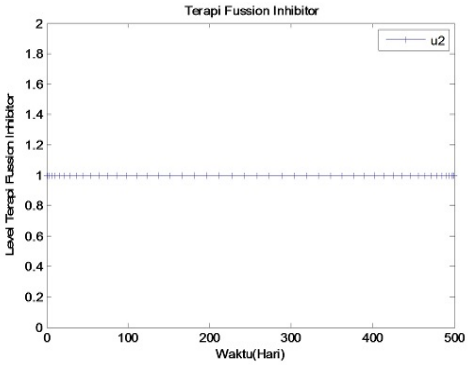


(iv) Productively infected T_h cells (wild type) (x_4)

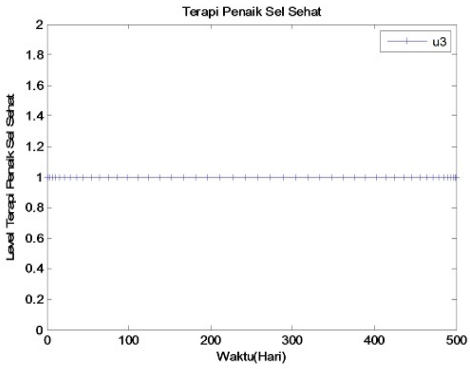
Figure 5: The case of the HIV virus ppopulation with an initial value $u_1 = u_2 = u_3 = u_4 = 1$ and the level of resistance mutans $a_{11} = 0.6$



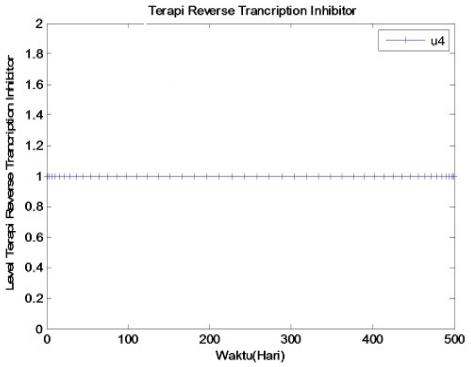
(i) *Protease inhibitor* therapy (u_1)



(ii) *Fussion inhibitor* therapy (u_2)



(iii) T_h cell enhancer therapy (u_3)



(iv) *Reverse trancription inhibitor* therapy (u_4)

Figure 6: Treatment of HIV with the initial value $u_1 = u_2 = u_3 = u_4 = 1$ and the level of resistance mutants $a_{11} = 0.6$

Table 2: Comparison of Simulation Results Without Therapy and the Treatment

No	Parameters	With Therapy		
		Analytic		Numerical
		Linearized at the equilibrium point	Optimal point linearization on numerical results	
1	The final number of wild-type HIV	Not defined	Not Defined	0
2	The final number of uninfected T_h cells	Not Defined	Not Defined	998.6436
3	The final number of proviral T_h cells (wild type)	Not Defined	Not Defined	5.9548×10^{-7}
4	The final number of productively infected T_h cells (wild type)	Not Defined	Not Defined	8.253×10^{-9}
5	The final number of mutant HIV strain	Not Defined	Not Defined	0.0055
6	The final number of provial T_h cells infected by the mutant strain	Not Defined	Not Defined	0.0026
7	The final number of T_h cells productively infected by the new strain	Not Defined	Not Defined	3.2614×10^{-6}

of numerical simulations for controlling the spread of the HIV virus to the initial time $t_0 = 0$ and the final time $t_f = 500$ successfully minimize mutant HIV strain (x_5), proviral Th cells infected by the mutant strain (x_6), and T_h cells productively infected by the new strain (x_7) as well as minimizing the cost of therapy is needed. The optimal solution indicates an increase in uninfected T_h cells and a decrease in wild-type HIV, proviral T_h cells (wild type), productively infected T_h cells (wild type), mutant HIV strain, proviral T_h cells infected by the mutant strain and T_h cells productively infected by the new strain. These results showed a significant difference with the analytical solution. There are many potential differences in the results, including as a result of linearization at the equilibrium point and the condition number for the matrix involved in the analytic solution.

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Miksalmina: Mathematics Graduate Study Program, Syiah Kuala University, Banda Aceh-Indonesia

Said Munzir: Mathematics Graduate Study Program, Syiah Kuala University, Banda Aceh-Indonesia
smunzir2001@yahoo.com

Tarmizi: Mathematics Graduate Study Program, Syiah Kuala University, Banda Aceh-Indonesia